

Univ. of Calif.

N63-203-62

Reprinted from EXPERIMENTAL NEUROLOGY
Copyright © 1963 by Academic Press Inc.

Volume 7, Number 3, March 1963
Printed in U. S. A.

EXPERIMENTAL NEUROLOGY 7, 186-209 (1963)

N63 17728

Code - none

Application of Phase Detection and Averaging Techniques in Computer Analysis of EEG Records in the Cat

W. R. ADEY AND D. O. WALTER¹

*Departments of Anatomy and Physiology, Brain Research Institute, University of
California at Los Angeles, and Veterans Administration Hospitals, Long Beach
and Los Angeles, California*

Received October 22, 1962

17728 over

Consistency of phase patterns in EEG records from the hippocampal system and midbrain reticular formation have been examined in the course of behavioral training in five cats with implanted electrodes. These studies have involved novel application of computing techniques, including continuous measurement of phase and amplitude characteristics of single wave trains by digital filtering techniques, the use of cross-spectral analyses with calculation of complex transfer functions, and averaging of records during repeated behavioral performances with calculation of coherence functions in cross-spectral examinations. It was found that rhythmicity appeared in the computed average at the rate of the dominant EEG frequency as T-maze performance reached a high level, and was related to a reduction in scatter in phase patterns at high performance levels. Reversal of behavioral cues was associated with an immediate brief increase in rhythmicity of the average, then a decline followed by a progressive reemergence of rhythmicity at the end of retraining. Continuous phase-and-amplitude examinations during delayed response performance indicated a rhythmic phase modulation on wave trains with an apparently single frequency appearing during periods of discrimination. Comparison of probability bounds in cross-spectral analysis with use of a polar coordinate display have indicated major differences in phase relations between different hippocampal regions between correct responses in certain circumstances, with consistency in different examinations. These findings are discussed in relation to a stochastic model of the cerebral

¹ These studies have been supported by grant B-1883 from the National Institutes of Health, and by grant AF-AFOSR 61-81 from the U.S. Air Force Office of Scientific Research, and by a grant from the National Aeronautics and Space Administration. Dr. E. Blum and Mr. Dan Brown, of Space Technology Laboratories, Inc., have been of vital assistance in some of the computer analyses. We gratefully acknowledge the assistance of Miss Cora Rucker and Miss Arlene Koithan in the histological controls, and the assistance of Mrs. Martha Satin in preparation of computer data files. Miss Hiroka Kowta has prepared the illustrations.

system, with reference to the possible role of the wave process in handling and storage of information.

Introduction .

The relationship of electrical wave processes in cerebral systems to the handling of information in these systems has long been a matter of conjecture. The apparent lack of precision in wave patterns accompanying defined behavioral acts has encouraged the view that they may be no more than essentially random processes, having at best only a broad relationship to states of consciousness or levels of emotional activity. On the other hand, increasing sophistication in the application of techniques of computer analysis to brain wave data recorded in learning situations has indicated a strong possibility that certain signatures in the wave processes do indeed carry a strong correlation with the transaction of information in those cerebral systems closely implicated in the learning process (1, 2, 4, 8, 9, 13). This relationship has been detected in the foregoing studies particularly in the hippocampal and amygdaloid systems of the temporal lobe and in those diencephalic zones, such as the subthalamic and midbrain reticular areas known to have major connections with these basal temporal cortical zones (5, 7).

Two fundamentally different approaches have been used in the present study. One has involved an examination of the rhythmic trains of waves, seen in the hippocampal system in the course of a discriminative motor act, for small amounts of phase or frequency modulation occurring about an essentially single "carrier" frequency. Such modulation would provide a possible means of information processing in any given cortical domain, particularly if the neurons exhibited a sensitiveness to changing patterns of phase, as has been discussed in detail elsewhere (4, 8). The technique used here is an application of a mathematical analysis devised by Goodman (15), which has been successfully applied to the detection of small amounts of phase modulation in other situations, such as that occurring in the magnetometer readings from a spinning satellite in space, as it advances through minor variations in the earth's magnetic field.

The second technique has utilized averaging methods to detect the progressive appearance, in the course of the acquisition of a learned discriminative task, of phase-locked components in EEG records taken during training. Both the behavioral performance and the phase-locked EEG components were repeatedly disrupted by reversing training cues, thus necessitating the formation of a new learned habit.

Neither of these computing methods has been previously applied to

the analysis of EEG data, and they appear to be useful additions to the usual armamentarium of techniques for the examination of a variety of physiological data in analog form. In addition, attention has been directed to the development of techniques for displaying on polar coordinates readouts of phase information from cross-spectral analyses performed on EEG data from discriminative situations, as described elsewhere (8).

Material and Methods

The data presented have been taken from five adult cats, with an average weight of 3.5 kg. The behavioral training and electrophysiological techniques were identical with those in more than 100 animals similarly implanted with cortical and subcortical electrodes in the past 4 years. Bipolar stainless steel electrodes were placed in dorsal and ventral zones of the hippocampus, and in the septum, amygdala, subthalamus and midbrain reticular formation. The recording dipole in each instance was formed between the bared tips of two 36-gauge stainless steel wires which projected 3 to 5 mm beyond the end of a 22-gauge nichrome wire supporting staff. All placements were made stereotaxically and confirmed histologically (8).

These animals were trained in a modified T-maze to make a visual discrimination, and in a delayed response performance, as described elsewhere (8, 17). In the T-maze test, the approach was to a concealed food reward on the basis of a visual cue, with an initial direct approach to the illuminated side of the maze as a requirement for the food reward. Delayed response training involved approach along one or other arm of a vee-bridge about 1 meter long, to a food reward concealed under one of two identical cans placed at the respective ends of the bridge arms. Approach to the food was permitted only after a delay of 5 or 10 sec following concealment of food. In this paradigm also, the approach was rewarded only if the initial approach was directly to the side of concealment. In both types of training, either thirty or forty presentations were made each day. The delayed response performance appeared to relate quite closely to the integrity of processes of recent memory, whereas the T-maze performance appeared linked to long-term memory of patterns of discriminative motor behavior.

Acquisition of data in analog form involved two primary systems. In all cases a conventional eight-channel paper written EEG record was made of each behavioral test epoch with a Grass Model IV electroenceph-

alograph, and included periods before and after the discriminative performance. The programming of behavioral cues was provided by pulses and step functions from a series of Grass stimulators, and these markers were available on the paper record. The programming sequence could be initiated, after an appropriate delay, by starting the EEG paper drive, or by independent manual control.

The magnetic tape recording system was developed in this laboratory, and uses a narrow band FM multiplex system, with standard IRIG telemetry subcarrier oscillators, and with the capability for recording twenty-eight channels of data on a twin-track recorder. Since particular importance attaches to the ready automatic detection of the separate episodes of each test epoch (such as predelay, delay period, and approach period), the step functions indicating these episodes were recorded as appropriately different d-c levels to permit their easy selection in subsequent data reduction.

Conversion of the analog paper records to digital form was accomplished by manual digitization on IBM punch cards, using a Benson Lehner Oscar converter. With this system, the maximum useful sampling rate was found to be at around 40 samples per sec. Despite the limitations thereby imposed on the upper reliable limit of spectral resolution, much useful readout was obtained with this technique in phase measurements by both cross-correlation and cross-spectral techniques. This technique of manual digitization has also been extensively applied to the further computation of cross-correlation and cross-spectral functions in the average response computations from the Mnemotron CAT computer as described below.

Magnetic tape records were digitized in the high-speed converter system at the facilities of Space Technology Laboratories, Inc. This system prepared a digital tape in IBM format for subsequent presentation to IBM 7090 computers. Sampling rates were normally 167 points per sec per channel. An editing and searching routine permitted the selection of any one or any group of the digitized epochs corresponding to each behavioral performance for presentation to the computer. Further fractionation of the selected material was possible on the basis of the flagging marks provided within each behavioral epoch as described above.

The nature and the site of the performance of the computations was essentially related to their inherent complexity. Much "on-line" computation of averaged EEG responses has been performed with the Mnemotron CAT computer, with readouts at twenty and forty averagings each day.

The readout was graphed either with a Sanborn recorder or an X-Y plotter. More elaborate computations, including cross-correlation, cross-spectral and phase-and-amplitude analyses, were performed on IBM 7090 computers at our Campus Computing Facility and at the facilities of Space Technology Laboratories, El Segundo, California. Computer readouts at these institutions were mainly by utilization of high-speed printers to give a graphical display. This greatly simplified the inherent problems of "data multiplication," rather than "data reduction," so commonly accompanying time series analyses with these forms of computer codes.

Results

AVERAGE RESPONSE COMPUTATIONS

A standard technique of analyzing the EEG records from the training periods was adopted. The computer provided a master pulse at the beginning of its 2-sec analysis epoch. The pulse was used to initiate the presentation of the behavioral situation 300 msec after initiation of the input to the computer.

A typical training record is shown in Fig. 1. It will be seen that certain characteristic rhythmic wave processes appear in the course of the discriminative approach to the food reward. In the dorsal hippocampal (LDH and RDH) and entorhinal cortical leads (L. ENT and R. ENT), the high-amplitude slow wave activity, which covered a wide spectrum from 4 to 7 cycle/sec in the preapproach epoch, regularized to an essentially single frequency around 5 cycle/sec during the discriminative performance. At the same time, certain rhythmic processes, less regular and less constant, appeared in subcortical structures, including the midbrain reticular substance and the subthalamus. These findings have been described in detail elsewhere (3, 4, 9, 17).

Three general types of averaged records were observed. In some, there was very little evidence of a rhythmic process time-locked to the situational presentation. In others, a clearly rhythmic readout was observed, with the dominant frequency similar to that of the EEG wave burst. A third group exhibited a rhythmic average at a slower rate than that of EEG dominant frequencies as indicated by visual inspection of the records, and by previous correlation studies (8). Many of these differences were related to levels of performance, and will be described below. In some instances, the appearance of slower rhythmic components in the average was interpreted as an index of a mathematical transform

of the EEG, with the possibility that it might constitute the basis of a "second-signal" system, and perhaps of fundamental importance in the transaction of information in cerebral tissue.

Changes in Computed Average in the Acquisition of Learned Discrimination. The following account of computed averages of EEG records concerns the progressive changes during T-maze training. To exclude as far as possible variations in computed average which might be at-

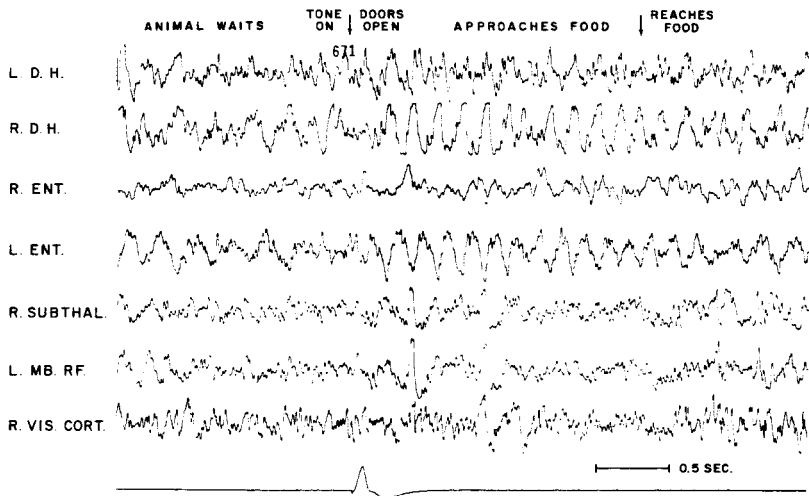


FIG. 1. Typical records in T-maze test, showing regularization of waves in hippocampus (L.D.H. and R.D.H.) and entorhinal cortex (L. ENT.) during approach to dark for food; cat WAD 37 (trial 17). Abbreviations: L.D.H. and R.D.H., left and right dorsal hippocampi; R. ENT. and L. ENT., right and left entorhinal cortex; R. SUBTHAL., right subthalamus; L. MB. RF., left midbrain reticular formation; R. VIS. CORT., right visual cortex.

tributable to varying latency of behavioral response, we have included only those computations made after establishment of a relatively stable behavioral response pattern with approach to food completed in approximately 1.75 sec. This pattern was established at a time when discriminative capability remained around chance level.

The progressive changes in the computed average during the initial paradigm of approach to the lighted compartment for food reward are shown in Fig. 2. With performance at levels between 50 and 80 per cent, the average from the left and right dorsal hippocampi showed some

rhythmicity at 5 cycle/sec. This rhythmicity was apparent on many days as separate trains appearing immediately after the doors opened and again towards the end of the analysis epoch. These waves were not as regular, nor of such high amplitude as those appearing toward the end of training.

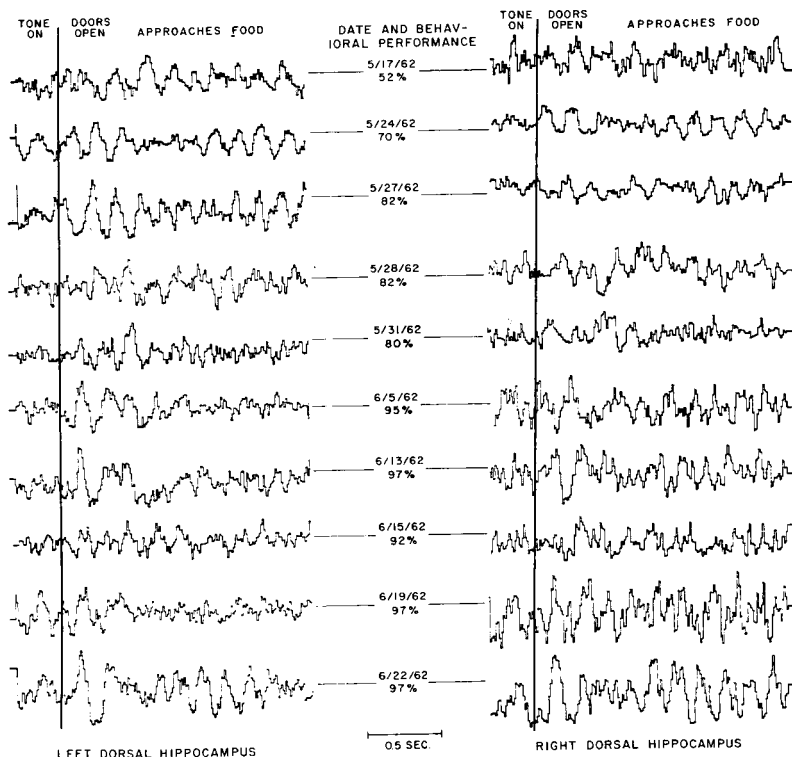


FIG. 2. Computed averages of records from left dorsal hippocampus (left column) and right dorsal hippocampus (right column) in 40 daily trials in the initial paradigm of approach to light for food reward; cat WAD 37. Note emergence of highly rhythmic average in late portion of average in bottom traces.

In the course of subsequent training, rhythmicity at the 5 cycle/sec rate seen in the primary EEG records became less obvious in the averaged readout, at performance levels between 80 and 90 per cent. It may be emphasized that this dropout in the rhythmicity of the averaged readout in no way reflected a decline in the amplitude or apparent regularity

of the 5 cycle/sec burst appearing with each approach in the individual EEG records. It thus appears to have resulted either from a loss of a locking of these bursts in a phase-related fashion to the onset of the situational presentation, or, perhaps, to the appearance of significant degrees of phase modulation on the 5 cycle/sec bursts. Variance in these patterns of phase modulation, as described below with a different computational technique, would account for these findings. With the attainment of a behavioral performance in the vicinity of 100 per cent, a greater degree of regular rhythmicity in the computed averages was noted than at any previous stage of training.

It may be observed in Fig. 2 that certain rhythmic averages, usually at 2 to 4 cycle/sec, appeared in some instances in the epoch prior to the presentation of the discriminative situation. These were traced in certain cases to unintentional cueing of the animal in the test situation, by such incidents as slight noises from the EEG paper drive, or by slight movements of the investigator producing unintended visual cues. This averaging technique proved itself exquisitely sensitive to the onset of unintended time-trace conditioning, and the utilization by the cat of very minor situational cues. Constant attention to this problem was necessary to eliminate unintended rituals in the behavioral procedures and chance cueing. Careful observation of the progressive average in the course of the training session indicated that in the absence of cueing, these rhythmicities in the pre-approach epoch behaved as random phenomena and became progressively smaller after ten and fifteen discriminations, whereas the rhythmic averages during the discriminative epoch grew progressively larger.

The subtle nature of the gradual increase in time-locked aspects of these EEG averages in the course of training is exemplified in Figs. 3 and 4 (from the second training paradigm, as described below). The sample records from the left and right dorsal hippocampi contributed to the computed averages shown at the bottom of each figure. The performance level in Fig. 3 was 75 per cent, and the average was essentially devoid of rhythmicity. By contrast, the computed average in Fig. 4 shows a highly rhythmic output in an identical test 20 days later, although the performance still remained at about the same level. Visual comparison of the EEG records from the two tests does not indicate significant differences in amplitude or regularity of the 5 cycle/sec wave trains.

Effects of Reversal of Cues on EEG and Performance. With the attainment of a performance level about 100 per cent, a switch was made to

food rewards placed on the unlit side of the T-maze box for the animal already described in Figs. 2, 3 and 4. This was followed by an immediate decrease in performance to considerably below chance level (Fig. 5), for the next two training days. In this respect, this animal differed from three other normal animals similarly subjected to repeated reversal of

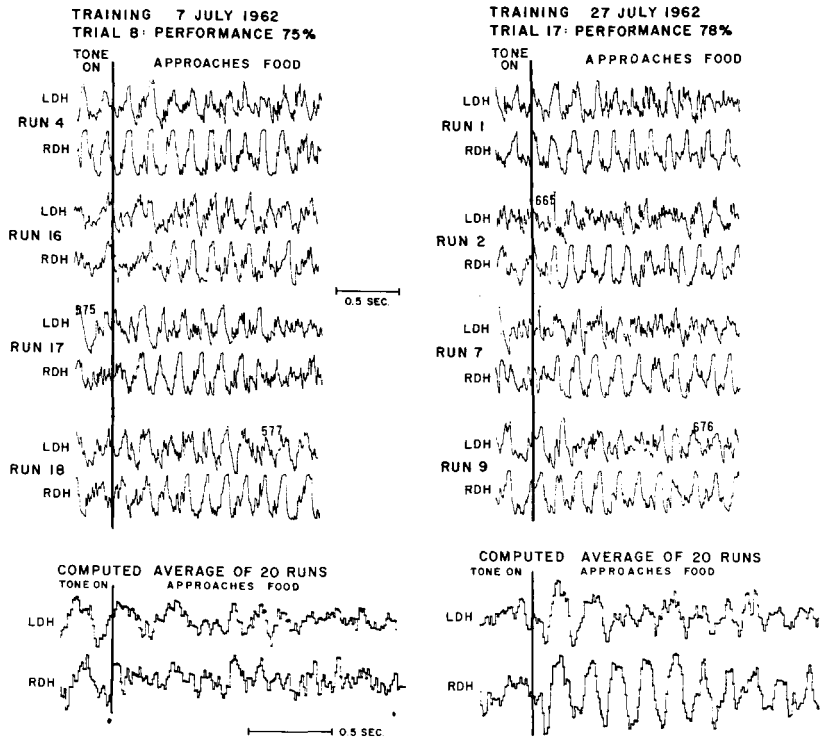


FIG. 3. Left: Representative EEG records with computed averages from twenty of these traces at midtraining in second paradigm. Note irregular character of averages.

FIG. 4. Right: From same animal as in Fig. 3, later in training in same paradigm. Note regularity of computed averages.

visual training cues. Typically, performance dropped only to chance levels on cue reversals, even on early training days.

Very striking changes were observed in the computed averages with this reversal of cues (Fig. 5). A very high amplitude average at 5 cycle/

sec was sustained throughout the approach epoch. It may be emphasized that no increase in amplitude of the 5 cycle/sec wave trains in the individual EEG records was noted at this time, so that the increase in averaged output apparently resulted from diminished scatter in phase patterns in consecutive performances.

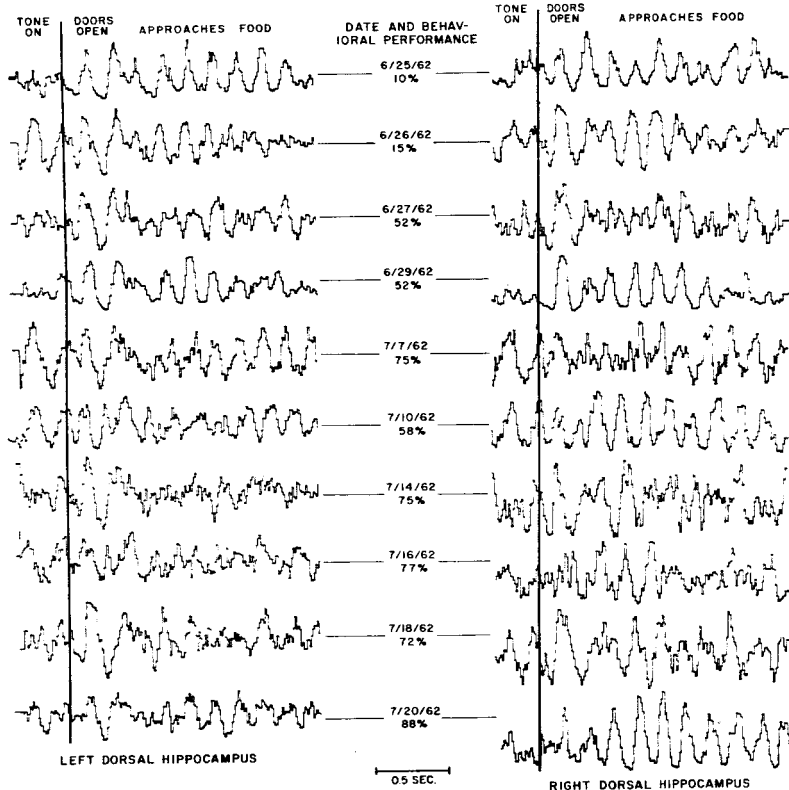


FIG. 5. Computed averages from same animal as in Fig. 2, during retraining to approach to dark cue instead of light. Highly rhythmic averages occurred immediately following reversal of cues, then declined but reappeared in late retraining.

It was observed that a progressive decline occurred in the amplitude and regularity of the 5 cycle/sec rhythmic component of the computed average in the ensuing days of training, with performances ranging from 52 to 77 per cent (Fig. 5). However, the rhythmicity persisted in greater degree during this retraining period than in the comparable levels of the

initial training (Fig. 2). The results indicated a certain "fly-wheeling," in the persistence of stable wave patterns established at the end of the initial training paradigm into the early days of the new test situation. With the ultimate attainment of a performance level of 88 per cent in this approach to the unlit area, a highly rhythmic average once again appeared.

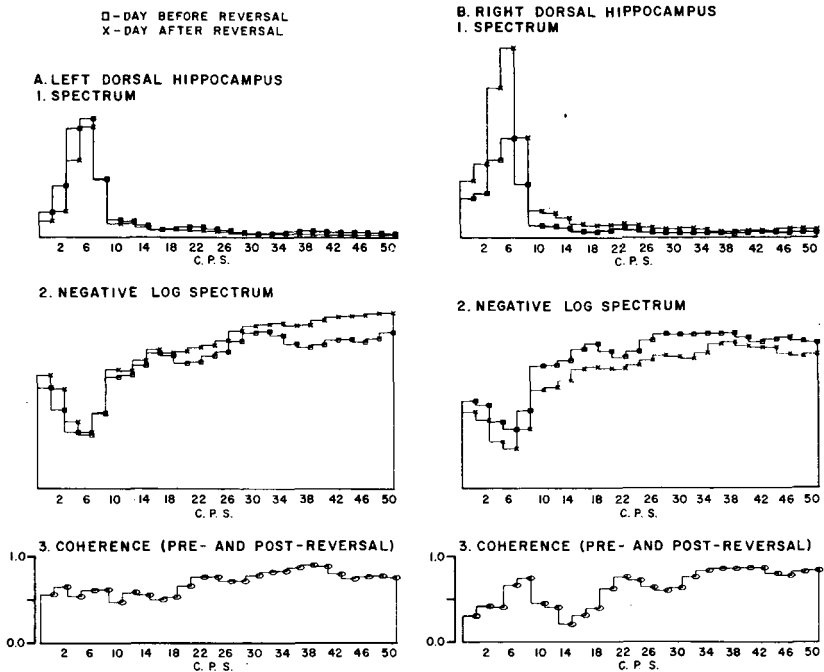


FIG. 6. Spectral analysis (1 and 2) of records from same animal in Figs. 2 and 5, with coherence values (3) between pre- and post-reversal records (see text).

We have initiated a variety of spectral examinations of these computed averages, particularly to assess possible differences between records prior to the following reversal of behavioral cues (Fig. 6). No major difference has been discerned in either spectral or log-spectral examinations. The maximum power in each case lay in the 5- to 6-cycle portion of the spectrum. Cross-spectral examinations of all these records showed high values of coherence in this same band between the left and right hippocampal averages from the same day, and slightly smaller values between identical structures on different days.

It may also be noted that coherence values remained high in the higher frequency portions of the spectrum (Fig. 6). Energy levels were low in this part of the spectrum. For this reason the technique of logarithmic spectral display was introduced to make manifest any minor energy peaks that might be concealed in the conventional spectral display. Such peaks have not so far been detected. The results of more extended examination of these findings will be presented elsewhere. This animal's training was not carried into the range of overtraining, where another decrease in rhythmicity of the computed average might have been anticipated (see below).

Effects of Repeated Reversal of Cues on Behavior and Computed EEG Averages. Over a period of 8 months, one animal was successively trained to approach lit and unlit compartments with seven consecutive reversals of cues. The results were in agreement with those described above in detail in the initial training and reversal. The behavioral performance consistently dropped to about 50 per cent immediately after the cue reversal, and rose progressively thereafter. The computed averages of dorsal hippocampal records increased in rhythmicity as performance reached a high level, and were sustained or further augmented in this regularity for 1 or 2 days following reversal of behavioral cues. Averages in subthalamic and midbrain reticular records, computed on alternate training days with the hippocampal records, showed similar changes.

The effects of repeated reversal of behavioral cues on the computed averages of midbrain reticular records is shown in Fig. 7. With the animal already trained to a 95 per cent level in its fourth training paradigm (approach to light), rhythmic waves at 3 to 4 cycle/sec were well developed in the average (Fig. 7A). These waves declined to a low level with reversal of the behavioral cues, but gradually reappeared with retraining (Fig. 7B). This sequence of changes was repeated in the sixth paradigm, with approach once more to light (Fig. 7C). With yet another reversal (Fig. 7D), there were indications of a sophistication in the situation, with a rapid rise in performance to over 90 per cent in the first four trials. The reticular records did not regain a rhythmicity comparable with that in earlier tests, even at performance levels over 95 per cent.

CONTINUOUS MEASUREMENT OF PHASE AND AMPLITUDE

Although the foregoing monitoring of components in the EEG record, which are time-locked to the presentation of the situation in successive

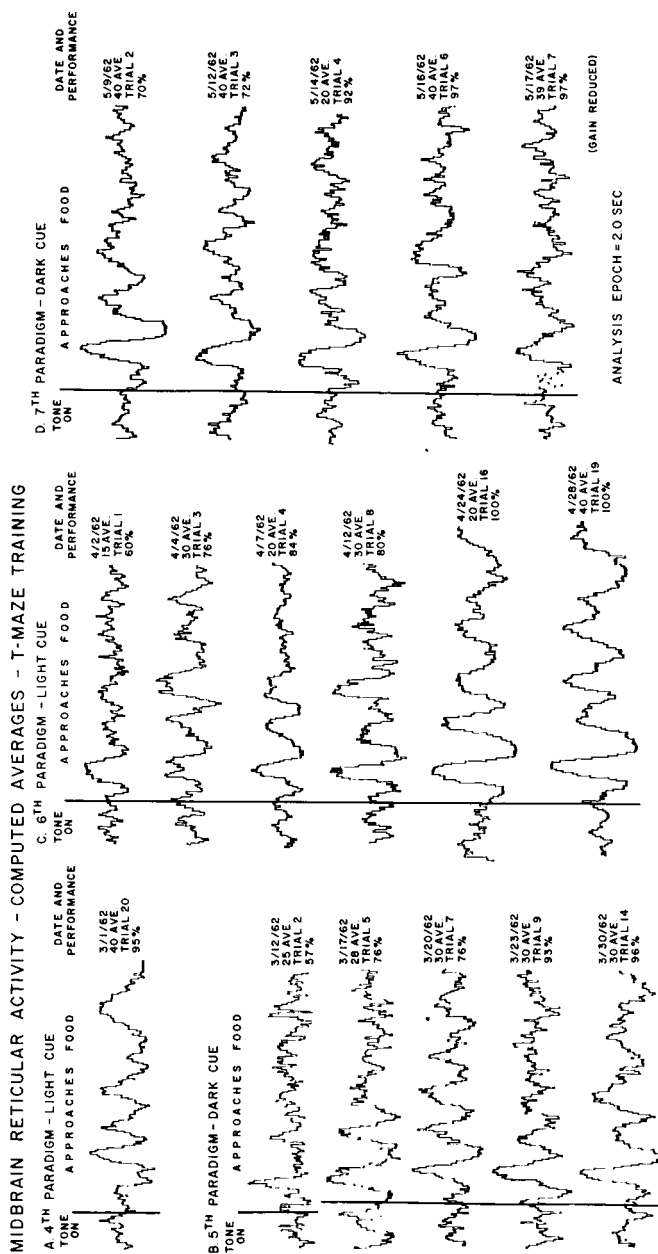


Fig. 7. Averages of records from midbrain reticular formation in successive reversals of training cues, first to light (A), then successively to dark (B), light (C) and dark (D).

behavioral performances, provides some measure of the stability of phase patterns in the wave trains, it cannot provide specific information as to the shift in phase (or frequency) of the wave train about a central or dominant frequency. These modulations in frequency may be occurring during the high-amplitude trains of apparently regular slow waves appearing in the hippocampus, and in certain subcortical regions, including the midbrain reticular formation, during the discriminative performance. This phase modulation might provide yet another parameter by which information might be handled in the cerebral system.

We have used the technique of digital filtering developed by Goodman (15). Appropriate mathematical coding establishes the digital computer as a bandpass filter, and allows the specification of the filter character-

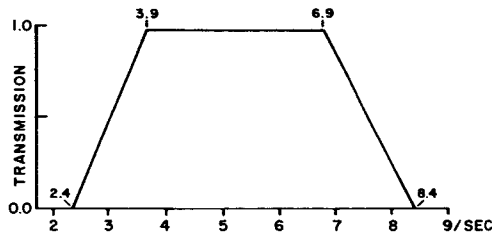


FIG. 8. Transmission characteristics of digital filter established to test phase and amplitude characteristics of single wave trains shown in Fig. 9.

istics in an extremely precise fashion. The filter characteristic can be established and modified with respect to flat-top width as well as shoulder and skirt characteristics. We have used a filter as shown in Fig. 8 to examine the phase and amplitude characteristics of hippocampal wave trains during delayed response performance (Fig. 9). The flat-top portion of the filter characteristic lay between 3.9 and 6.9 cycle/sec, and the phase shift introduced by the filter was precisely zero throughout this band. It may be emphasized that this flat, in-phase characteristic is extremely important if ambiguities in the computed readouts of phase and amplitude are to be avoided.

It was found that, in the waiting interval between food concealment and the lowering of the bridge in the delayed response test, the hippocampal EEG showed a wide spectrum of frequencies varying between 3 and 6 cycle/sec. During the discriminative approach to food, the waves regularized to a narrow band between 5.0 and 6.5 cycle/sec. These findings have been described in detail elsewhere (4, 17).

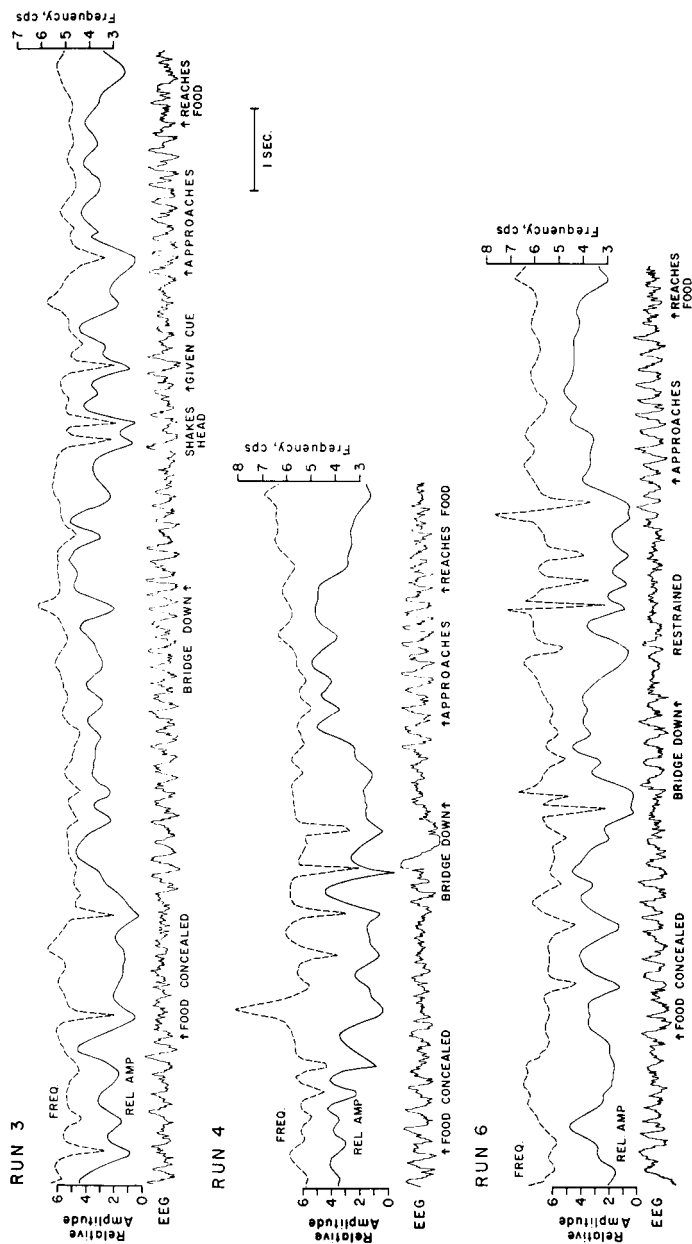


Fig. 9. Continuous measures of frequency (or phase) modulation and relative amplitude in wave activity of a single dorsal hippocampal lead in delayed-response performance using digital filter of Fig. 9; cat WAD 31. In each of the three analyses shown, the animal first sees food concealed and awaits lowering of bridge before discriminative approach is permitted (17). Note rhythmic frequency modulation on wave trains during approach to food, as well as irregularly during waiting period.

Computer analysis of entorhinal EEG records in three different delayed response tests are shown in Fig. 9. The frequency modulation, and thus, the phase shifts, of the wave trains around a filter center frequency of 5.4 cycle/sec are depicted simultaneously with the EEG record in each trial. Simultaneous and continuous measurements of relative amplitude were also plotted.

It will be seen that wide excursions in frequency and amplitude occurred in the waiting period in each of the three trials. Brief transient declines in the dominant frequency to a value below the filter pass band occurred in this period, and amplitude values dropped equally suddenly and briefly in many instances. The fact that the majority of the frequency transients are toward lower frequencies allows one to infer that each new burst of slow-wave activity appears in later phase than would have obtained, had the previous burst continued. It is as if the termination of one burst were the stimulus for the appearance of a new one, although of course such a speculation would require much more support than is presently available.

By contrast, the frequency record during the discriminative approach confirmed previous findings of a narrow spectrum of activity between 5 and 6 cycle/sec, and also clearly indicated a rhythmic frequency or phase modulation at 1 to 2 cycle/sec on this "carrier" frequency of 5 cycle/sec. Moreover, the relative-amplitude readout was maintained at a high level during the discriminative epoch, and frequently showed amplitude modulation at much the same frequency as the phase modulation. It should be emphasized that great care has been taken to eliminate possible interaction between amplitude and frequency modulation components in the mathematical analysis, so that although these phenomena occur simultaneously at essentially identical rates, they should each be regarded as validly detected and independent of each other.

The value of digital filtering as a powerful tool in problems of wave analysis, and its particular ability to give a continuous measure of phase and amplitude parameters in a single wave train, is exemplified by these findings, and will be discussed further below.

USE OF COMPLEX TRANSFER FUNCTION AND POLAR COORDINATE DISPLAYS IN CROSS-SPECTRAL ANALYSIS

Our previous studies have indicated that certain phase patterns between wave trains in different parts of the hippocampal system may shift in a repeatable fashion, when the fully trained animal makes an

occasional incorrect response (8). Cross-correlation analysis indicated highly consistent, but different, phase patterns in both correct and incorrect responses. These findings were supported in cross-spectral analyses, which indicated greatly different phase patterns between records from two hippocampal regions in the course of correct and incorrect responses.

As a useful extension of these analyses, a technique has been developed² to display the phase relations between EEG records from two different regions as a polar plot. This method permits a display of phase relations between two records across a spectrum of frequencies. Also, by calculation of complex coherence functions, the probability bounds are established that shared energy levels in any portion of the spectrum will lie within specified phase angles. At the same time, the radial dimension of the plot is used to indicate the amplitude transfer function between these records and its probable bounds.

This method provides a striking display of the shifts in phase patterns between correct and incorrect responses in T-maze testing, in further analysis of data from a fully trained animal already examined for such differences by cross-correlation and cross-spectral methods (7). It will be noted (Fig. 10) that the same 6 cycle/sec band which shows the maximum energy peak in the two records separately is also that in which the transfer vector relating the hippocampal with the entorhinal waves is most narrowly limited, as indicated by the shaded areas. The boundaries of this and the other zones shown are established at the 50 per cent level of probability that the mean transfer vector lies within the zone delineated.

It is clear that there is good general agreement between the calculations relating to correct responses on two different days, in the phase relations at and near this best-related frequency. By contrast, the findings in incorrect responses from each of the same 2 days showed a totally different location for the 6 cycle/sec zones (Fig. 10A), although there was again good agreement between these incorrect responses in the location of those zones. The incorrect responses also showed a much wider scatter in the distribution of other spectral zones than was seen in the correct responses. A further example from a different animal (Fig. 10B) showed a major change in phase relations between entorhinal cortical and hippocampal records in correct and incorrect responses.

² This and other analytic techniques cited here were developed and tested by D. O. Walter in the course of thesis studies.

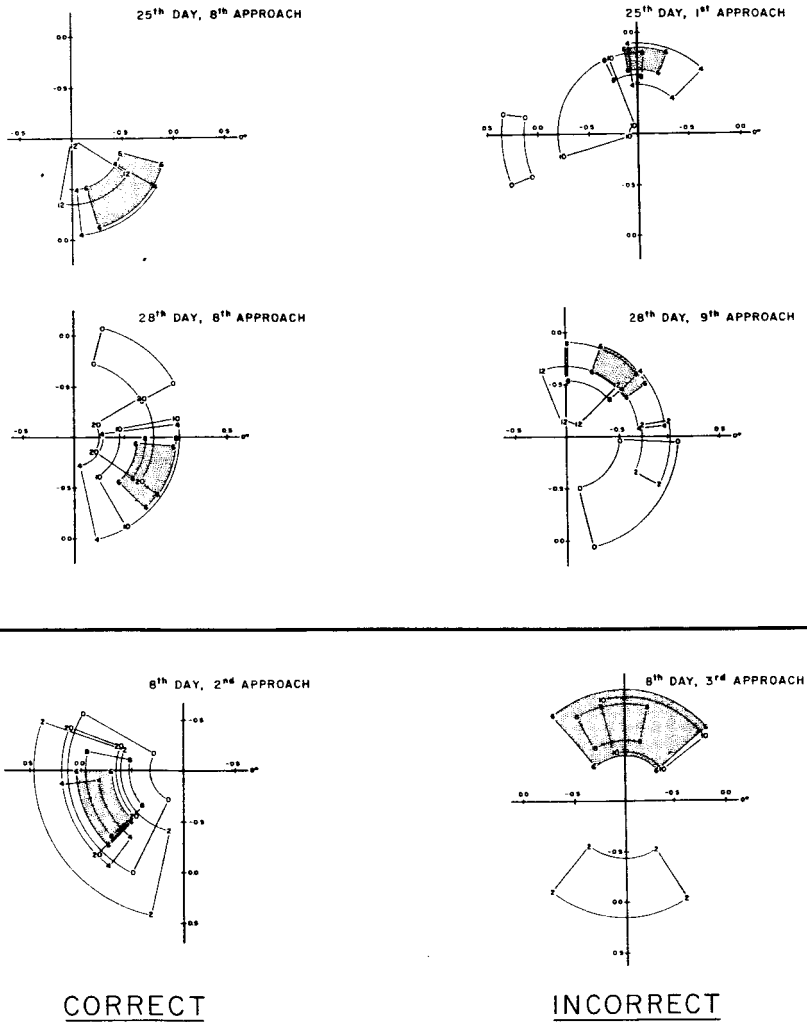


FIG. 10. Stochastic models of EEG. Examples of polar coordinate plots of probability bounds on complex amplitude transfer functions, dorsal hippocampus to entorhinal cortex. Phase angles are depicted on angular coordinates, and transfer functions are shown on radii. Shaded fans enclose 6 cycle/sec portions of spectrum, and are maximum energy zones. Note consistency between correct responses and differences from incorrect responses in one animal (above), and similar wide differences between correct and incorrect responses in another animal (below line).

We are currently interested in the extent to which such findings may reflect a general difference in phase patterns between correct and incorrect decisions in fully trained animals. Current studies in a limited series of analyses indicate that such changes do not always occur and that incorrect responses may be isophasic with the correct ones. This matter is receiving further study, particularly since the complexity of the behavioral response pattern involved in this discriminative task may underlie irregularities noted in some results of these spectral analyses.

Discussion

At this time, an increasing tide of published research concerns itself with mathematical models of nerve nets based exclusively on digital or pulse-coded operations, with the clear implication that activity in the net may appropriately simulate activity in cerebral neuronal systems. The neurophysiologist who is concerned with both computer analysis of neurophysiological data, and with the formulation of mathematical models based on these analyses, finds himself confronted with an endless array of models in which aspects of uniqueness of organization, both anatomical and physiological, which may relate to the singular capacity of cerebral systems to permanently store information, tend to be completely ignored.

The hypothesis has been advanced elsewhere (1, 2, 3, 8, 9) that the rhythmic wave process characterizing activity in many cortical and subcortical cerebral structures may be fundamentally correlated with the ability of these tissues to undergo permanent changes in excitability as a result of their prior participation in specified patterns of excitation. In an anatomical frame, our attention has been directed to the association between the characteristic phenomenon of dendritic overlap in palisades of cells characterizing all vertebrate cerebral ganglia, and the concurrent development of a rhythmic electric wave process. There is a noteworthy absence of dendritic overlap in such "nonlearning" structures as the spinal cord, and, as Gasteiger (14) has pointed out, the slow components of spinal cord electrical activity appear to have an essentially irregular and random character. The origin of the wave process in longitudinal electronic gradients sweeping from the dendritic tree towards the cell body has been proposed by Green, Maxwell, Schindler and Stumpf (16), and we have discussed the possibility that the cell may function as a phase-comparator of waves arising "intrinsically" with those reaching the cell "extrinsically" (8), or that it may exercise this

comparator function in relation to complex spatio-temporal wave patterns sweeping across its surface. In either case, the initiation of cellular firing might depend on the precise recurrence of a spatio-temporal wave pattern, to which the neuron had been previously exposed, and which might determine the permanent physicochemical change underlying the "memory trace" (6).

The present study has attempted to define, by several techniques not hitherto applied to the examination of electrophysiological data, components in the apparent imprecision of EEG records which are either phase-locked in leads from circumscribed cortical or subcortical zones in relation to the repeated performance of a learned motor task, or which may have constant phase relations to wave patterns appearing simultaneously in other cortical or subcortical localities, or which may have aspects of phase or frequency modulation on a "carrier" wave train appearing in the course of attentive or discriminative behavior. It is obvious that any one of these three possibilities would provide a frame in which either the nerve cell or the organized cerebral system might adequately "sense" the informational basis of afferent volleys, and the data provide evidence that all three phenomena may have important roles in the various hierarchies from the microcosm of the individual neuron to the macrocosm of complexly organized but profoundly interrelated cortico-cortical and cortico-subcortical systems.

More importantly, however, part of the evidence presented would appear to bear significantly on the fundamental nature of essential cerebral processes, viewed as either deterministic or probabilistic phenomena. Previous cross-correlation studies of EEG phase patterns in correct and incorrect responses (8) had indicated that the phase patterns in a population of correct responses displayed a considerable scatter about a mean phase displacement. Similar, but less extensive data in incorrect responses also showed such a scatter. The findings presented here in the complex transfer functions from cross-spectral analyses emphasize that the stochastic mode of operation is indeed a strong possibility in the handling of information on the basis of a wave process. Such a scheme would envisage the excitability of the individual neuron as depending not only on its previous experience of complex spatio-temporal patterns of waves, as outlined above, but additionally, would suggest that the effectiveness of any subsequent wave pattern in eliciting neuronal firing might depend on its multivariate relationship to an "optimal" wave pattern, capable of inducing firing of that neuron at its lowest threshold.

An examination of threshold phenomena in the auditory cortex of man has already been considered by Koshevnikov (21) using such a stochastic model, with the delineation of two statistically different populations of responses for sub- and suprathreshold stimuli by the use of Bayes' theorem.

Such a notion appears to significantly extend the basis for a mathematical model of the neuronal organization of cerebral systems over the more general unicellular considerations offered by Bullock (10) and others. There is, as yet, no categorical evidence relating the physiological events in any noncerebral neuronal system, or the phenomena in neurons in natural or artificial isolation from other nerve cells, to the essential processes of information storage. Whatever basis may ultimately be found for the physicochemical changes underlying the memory trace, it would appear that a comprehension and utilization of data relating this process to stochastic aspects of both neuronal firing patterns and the wave processes pervading the surrounding cortical domain may provide an exciting avenue directly approaching the essential question of the uniqueness of functional organization in the memory process.

Application of averaging techniques to changing patterns of electrical activity in the processes of attention and learning have rested largely on the evaluation of changing amplitudes of evoked responses to brief, repetitive stimuli presented in the same sensory modality as that primarily involved in the attentive or learning process (11, 12). The transient stimulus thus represents an intercurrent event in a continuous pattern of ongoing activity, and although these studies have disclosed clear differentials related to levels of alerting and learning (19, 20), it is difficult to see how such an intercurrent signal, even though it may use the same modality, necessarily involves the signal system on which the conditioning process rests (18, 22). For these reasons, recent studies have included attempts to average epochs of ongoing records. Morrell, Barlow and Brazier (23) observed a rhythmic average in visual cortical records in the rabbit in the CS-US interval at certain levels of training to pairings of tone flickering light. The computed average exhibited a rhythmicity at 4 to 5 cycle/sec, apparently unrelated to the subsequent flash stimulation at 10 per sec. This they attributed to activity in the underlying hippocampus.

Our application of averaging to the EEG during training has involved analysis of a 2-sec epoch, including the period of a visual discrimination. It is apparent from these results that with progressive increment in the

learned performance, a considerable degree of phase-locking to the onset of the situational presentation occurred in both hippocampal cortical and midbrain reticular records. Moreover, the progressive increment in the rhythmicity of the computed average appeared to arise from a gradual decline in the scatter of the phase patterns of individual EEG records, and not from an increase in amplitude of the wave discharges in individual records during discrimination. The exquisite sensitiveness of this technique to minor changes in phase-locking during repetitive performances has already been pointed out, and is exemplified by the quite sudden increment in synchronism immediately following reversal of behavioral cues, before the "degeneration" of the average into an essentially irregular phenomenon in the following days of retraining. It is obvious that the precise extent of the scatter in phase patterns at various levels of training could be satisfactorily examined by the application of the Goodman filter technique utilized in other aspects of this study. The results of such filtering studies will be described elsewhere.

Less clear in these averaging studies are the physiological mechanisms which might underlie the phenomenon noted in some, but not all, instances, as displayed in Fig. 7, of the failure of reappearance of a rhythmic average, even at a high training level, after repeated reversal of behavioral cues. In the absence of further data from filtering analyses, it can only be surmised that the essential information necessary to the discriminative performance may have reached minimal proportions, and that the indubitable behavioral sophistication engendered by such long training enables an appropriate behavioral performance with little more than fleeting attention to the behavioral cues. In these circumstances, a high scatter might once again appear in phase patterns of successive records, but having certain subtle differences from the irregular patterns in early training. Speculatively, the less regular pattern in the sophisticated animal may still contain certain key aspects of information, and represent a "shorthand," as noted above. In this connection, it is noteworthy that the averages in retraining following the first reversal of cues (Fig. 5) do not revert to the degree of irregularity seen in the initial training (Fig. 2) at any time during the retraining period.

Whatever may be the ultimate disclosure of the relationship between the cerebral wave process and the transaction and storage of information within the system, it has become apparent that, with increasing precision in the techniques which we can bring to bear on the wave process, there is growing reason to doubt that these waves are merely "noise," with a

randomness that rules them from serious consideration as the functional basis of the most intrinsic mechanisms in the cerebral system. Rather, it may be suggested that they provide a more than ample frame for integrative processes preceding, and not necessarily followed by, aspects of pulse-coded neuronal firing, and that the information-handling capability of such a double system would transcend any based on pulse-coded activity alone. At the heart of such a model must necessarily lie a stochastic frame, with equal importance probably attaching to the modulation of the electrotonic dendritic processes by nonlinear impedance loads in adjacent tissue, both neural and non-neural (6).

References

1. ADEY, W. R. 1961. Brain mechanisms and the learning process. *Federation Proc.* **20**: 617-621.
2. ADEY, W. R., F. R. BELL, and B. J. DENNIS. 1962. Effects of LSD, Psilocybin and Psilocin on temporal lobe EEG patterns and learned behavior in the cat. *Neurology* **12**: 591-602.
3. ADEY, W. R., and C. W. DUNLOP. 1960. The action of certain cyclohexamines on hippocampal system during approach performance in the cat. *J. Pharmacol. Exptl. Therap.* **130**: 418-426.
4. ADEY, W. R., C. W. DUNLOP, and C. E. HENDRIX. 1960. Hippocampal slow waves; distribution and phase relations in the course of approach learning. *A.M.A. Arch. Neurol.* **3**: 74-90.
5. ADEY, W. R., C. W. DUNLOP, and S. SUNDERLAND. 1958. A survey of rhinencephalic interconnections with the brainstem. *J. Comp. Neurol.* **110**: 173-204.
6. ADEY, W. R., R. T. KADO, and J. DIDIO. 1962. Impedance measurements in brain tissue of animals using microvolt signals. *Exptl. Neurol.* **5**: 47-66.
7. ADEY, W. R., J. P. SEGUNDO, and R. B. LIVINGSTON. 1957. Corticifugal effects on brainstem conduction. *J. Neurophysiol.* **20**: 1-16.
8. ADEY, W. R., D. O. WALTER, and C. E. HENDRIX. 1961. Computer techniques in correlation and spectral analyses of cerebral slow waves during discriminative behavior. *Exptl. Neurol.* **3**: 501-524.
9. ADEY, W. R., D. O. WALTER, and D. F. LINDSLEY. 1962. Effects of subthalamic lesions on learned behavior and correlated hippocampal and subcortical slow-wave activity. *A.M.A. Arch. Neurol.* **6**: 194-207.
10. BULLOCK, T. H. 1959. Neuron doctrine and electrophysiology. *Science* **129**: 997-1002.
11. BRAZIER, M. A. B., and J. S. BARLOW. 1956. Some applications of correlation analysis to clinical problems in electroencephalography. *Electroencephalog. and Clin. Neurophysiol.* **8**: 325-331.
12. BRAZIER, M. A. B., K. F. KILLAM, and J. A. HANCE. 1959. The reactivity of the nervous system in the light of past history of the organism, pp. 699-716. In "Sensory Communication," a symposium, edited by Walter A. Rosenblith, MIT Publication Series. John Wiley, New York.

13. FREEMAN, W. J. 1962. Linear approximation of prepyriform evoked potential in cats. *Exptl. Neurol.* **5**: 477-499.
14. GASTEIGER, E. L. 1959. The electrogram in deafferented spinal cord. *Proc. XXI Intern. Congr. Physiol. Sci.*, Buenos Aires, p. 105.
15. GOODMAN, N. R. 1960. Measuring amplitude and phase. *J. Franklin Inst.* **270**: 437-450.
16. GREEN, J. D., D. S. MAXWELL, W. J. SCHINDLER, and C. STUMPF. 1960. Rabbit EEG "theta" rhythm; its anatomical source and relation to activity in single neurons. *J. Neurophysiol.* **23**: 403-420.
17. HOLMES, J. E., and W. R. ADEY. 1960. The electrical activity of the entorhinal cortex during conditioned behavior. *Am. J. Physiol.* **199**: 741-744.
18. HUBEL, D. H. 1959. Single unit activity in striate cortex of unrestrained cats. *J. Physiol. London* **147**: 226-238.
19. JOHN, E. R., and K. F. KILLAM. 1959. Electrophysiological correlates of avoidance conditioning in the cat. *J. Pharmacol. Exptl. Therap.* **125**: 252-274.
20. JOHN, E. R., and K. F. KILLAM. 1960. Electrophysiological correlates of differential approach-avoidance conditioning in cats. *J. Nervous Mental Disease* **131**: 183-201.
21. KOZHEVNIKOW, V. A. 1958. Some problems concerned with the measurement and analysis of EEG tracings and the theory of information. *Fiziol. Zhur. S.S.S.R.* **43**: 983-994.
22. MATURANA, H. R., J. Y. LETTVIN, W. H. PITTS, and W. S. MCCULLOCH. 1960. Physiology and anatomy of vision in the frog. *J. Gen. Physiol.* **43**: 129-175.
23. MORRELL, F., J. S. BARLOW, and M. A. B. BRAZIER. 1960. Analysis of conditioned repetitive response by means of the average response computer, pp. 123-137. In "Recent Advances in Biological Psychiatry." Grune and Stratton, New York.